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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,137	11/13/2001	Gijsbertus Franciscus Maria Verheijden	2355-133	6400

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,137	VERHEIJDEN ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11-16 are pending and being acted upon.

2. A review of the claims raises the question of whether of not Applicant intended that this application be filed as a Divisional or possibly a Continuation-in-Part (comprising some additional disclosure) because the claims do not seem to fit the specification. The specification discloses a method for "treatment of T-cell mediated articular cartilage destruction in autoimmune diseases," (page 1). The instant claims however, simply recite a method for "treating autoimmune diseases." Clearly, the claims as now recited are significantly broader than the disclosure of the instant specification. Applicant is invited to clarify this situation, however, Applicant is advised that it is the Examiner's position that the instant specification cannot support the instant claims as it does not disclose a method for the treatment of all autoimmune diseases as claimed.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

The method of the instant claims comprises inducing tolerance to a self-peptide as a treatment for an autoimmune disease. Note that the claimed method would encompass human

autoimmune disease, particularly rheumatoid arthritis (RA), and the administration of altered peptide ligands (APLs, because both SEQ ID NOS:1 and 2 are degenerate). Peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for RA) provided successful results in animal models, however, both were complete failures in human trials. Thus, the reference demonstrates that even unsubstituted peptides (peptides that are not APLs) that work in *in vivo* animal disease models cannot be expected to work in humans. Regarding the even more unpredictable APLs, Anderton (2001, page 370) teaches that "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders." Indeed, the reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients.

Further regarding the use of APLs in immunotherapy, Smilek et al. (1991), provides a demonstration of the unpredictability of APLs even in an animal model. The reference teaches that administration of an MBP peptide to an experimental animal induces EAE (an animal model of MS), whereas the administration of an MBP APL with a single substitution induces tolerance and protects the animal from subsequent disease induction. The authors theorized that a particular APL with two substitutions ought to also induce said tolerance. They found, however, that "in contrast to expectations, this peptide does not inhibit EAE." At a loss to explain the findings, the authors teach that the mechanisms of tolerance induction are "poorly understood." Thus, one of skill in the art would conclude from the work that the design of peptides for the induction of tolerance through immunotherapy must be considered at best to be highly unpredictable.

Given the established unpredictability of the art, the instant specification would require a significant teaching to be enabled. In particular, it is unlikely that any disclosure short of significant *in vivo* data would be able to overcome said established unpredictability. The instant specification provides just two *in vitro* examples. The first example merely discloses that some of the encompassed peptides bind two specific HLA DR molecules. The second example discloses that some of the

encompassed peptides are capable of inducing a proliferative response in PBMCs obtained from three RA patients. These examples are insufficient enablement given the unpredictability of the art and the breadth of the claims. There is no disclosure regarding the use of any APLs. There is no disclosure regarding the use of the claimed method for the treatment of any autoimmune diseases other than RA. Even regarding RA, there is no reasonable correlation between the *in vitro* data and an *in vivo* method of treatment. Accordingly, the claimed method is considered to be highly unpredictable and requiring of undue experimentation to practice as claimed.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 11-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of copending Application No. 09/710,977. Although the conflicting claims are not identical, they are not patentably distinct from each other because both

applications recite claims drawn to a method of treatment (or treating) autoimmune diseses comprising administering a tolerance inductive amount of identical peptides. Whereas the '977 application recites the administration of a pharmaceutical preparation of the peptides, and the instant application does not, a composition of the instant peptides administered to a patient would comprise a pharmaceutical composition given the definition of pharmaceutical as medicinal or comprising a drug.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Please Note: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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9/1/04
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